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Posture changes platelet inhibition time after ingestion of prasugrel

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ABSTRACT

INTRODUCTION: Several studies have suggested that supine posture during pill ingestion prolongs oesophageal transit time. Whether ingesting prasugrel in an upright position leads to reduced platelet reactivity during percutaneous coronary intervention remains unclear.

METHODS: A total of 20 people were randomly assigned to ingest 60 mg of prasugrel in either the supine or upright position. Platelet reactivity was analysed using the point-of-care assay VerifyNow.

RESULTS: In the upright position, the velocity of platelet inhibition was highest between 20 and 40 min. (Δ = 101.9 P2Y12 reaction units (PRU)). In the supine position, the highest value was seen between 40 and 60 min. (Δ = 56.85 PRU). Time to reach the cut-off for reducing peri- and post-operative risk of thrombosis showed a mean difference of 8 min. in favour of the upright group.

CONCLUSIONS: A trend towards faster reduction of platelet reactivity was seen when ingesting prasugrel in the upright position compared with the supine position.

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TRIAL REGISTRATION: This trial was registered with clinicaltrials.gov (NCT01365741).

The use of percutaneous coronary intervention (PCI) over fibrinolysis has been proven to reduce the mortality and morbidity for patients with acute myocardial infarction [1]. For PCI to have a positive effect on mortality, it needs to be conducted no longer than 90-120 min. after the first medical contact [2].

Numerous studies have proven the importance of reducing pre- as well as post-procedural platelet reactivity in patients undergoing PCI [3, 4]. Efforts have been put into finding a "cut-off" target value for point-of-care (POC) assays of platelet reactivity used to evaluate the risk of complications after PCI [5-7].

The oral thienopyridine, prasugrel, has been proven to be superior to clopidogrel in the treatment of patients with acute coronary syndrome due to a faster and more consistent platelet inhibition [8]. Prasugrel is a prodrug that is metabolised to one active metabolite (R-138727) and numerous inactive metabolites by the hepatic cytochrome P450, isoenzymes CYP3A4, CYP2B6 and, to a lesser extent, CYP2C9 and CYP2C19. The active metabolite binds irreversibly to the platelet P2Y12 ADP receptor and inhibits platelet aggregation.

Previous studies have shown that the passage of tablets through the upper gastrointestinal tract is highly variable and dependent on multiple factors including body posture at the time of ingestion [9-12]. In one study [10], 58% of tablets swallowed in the supine position stayed in the oesophagus for more than 5 min. Posture may influence the pharmacokinetics of orally administered drugs by affecting the rate of gastric emptying, intestinal motility, absorption, splanchnic-hepatic blood flow, renal elimination, plasma volume and metabolism [13].

The purpose of this study was to investigate the difference in degree and velocity of thrombocytic inhibition between two different postures at the time of ingestion of 60 mg prasugrel.

METHODS

A total of 20 non-smoking, healthy males with no previous medical history aged 20-30 years participated in this study. All participants gave their written informed consent, and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. The Danish National Committee on Biomedical Research Ethics and the Danish Data Protection Agency approved the study (identification number H-15011038).

Blood sampling: Before each experiment, a 1.7 mm (16 gauge) plastic indwelling catheter was inserted into the v. mediana cubiti and connected to a three-way stopcock and a shielded blood-collecting needle via a 10-cc plastic tube.

At 20-min. intervals after ingestion of 60 mg of prasugrel, 2 ml of blood was drawn for VerifyNow analysis using a citrate Vacuette. Before sampling for analysis, 4 ml of blood were drawn on a K3 ethylenediaminetetraacetic acid (EDTA) tube, and after sampling the system was flushed with 0.9% saline.

Ingestion: A randomised cross-over trial with two phases and a two-week washout period was conducted. Participants were randomised at their first visit to either the supine or the upright position, and thus the re-

ORIGINAL ARTICLE

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TABLE 1

Baseline characteristics (n = 20).

Gender: male, %	100
Age, mean (range), yrs	23 (20-29)
Weight, mean (range), kg	74.7 (68-90)
Height, mean (range), cm	179.5 (176-190)
BMI, mean (range), kg/m^2	22.8 (20.7-24.9)
Ethnicity, %	
Caucasian of Danish descent	90
Danish of Persian descent	10

TABLE 2

The difference between supine and upright position after adjusting for baseline differences.

Time, min.	Difference in PRU, mean ± SEM (95% CI)	p-value
T0	65.76 ± 26.10 (-65.76-36.36)	0.570
T20	53.91 ± 26.05 (-53.91-48.21)	0.913
T40	102.11 ± 26.05 (-102.11-0.14)	0.050
T60	101.76 ± 26.05 (-101.76-0.36)	0.052
T80	98.91 ± 26.05 (-98.91-3.21)	0.066
T100	88.66 ± 26.05 (-88.66-13.46)	0.149

CI = confidence interval; PRU = P2Y12 reaction units; SEM = standard error of the mean.

verse position at their next visit. Participants randomised to the supine position were laying on a hospital bed with no head elevation. They were instructed to swallow 6 × 10 mg of prasugrel with the use of 50 ml of water, through a straw. Thereafter, they were instructed to lie as still as possible for the duration of the experiment.

The participants who were randomised to the upright position followed the same instructions, but ingested the pills sitting in an upright position. They maintained the upright position for 120 sec. and were then invited to lie down.

Platelet function testing: The antiplatelet activity of prasugrel was tested with turbidimetric optical detection (VerifyNow P2Y12 test; Accumetrics, San Diego, CA, USA) in citrate- anticoagulated whole-blood samples collected every 20 min. up to 100 min. The ADP-activated platelets aggregated in the test channel on fibrinogen-coated microbeads, and the resultant change in optical signal was measured and expressed as P2Y12 reaction units (PRU). In the control channel, platelets were activated with thrombin receptor-activating peptides, and the baseline maximal aggregation was measured.

Statistical analysis: The data were analysed using SPSS 20 software (SPSS Inc., Chicago, IL, USA). Repeated ANOVA measures were performed based on the difference calculated between the results for degree and velocity of thrombocytic inhibition in the supine and the upright position. The Wilcoxon signed rank test was used for calculation of differences in time to reach cut-off for PRU. A cut-off value for avoiding complications was set to ≤ 240 PRU. A p-value of < 0.05 was considered significant.

We also looked for the velocity of inhibition, being the delta values between two measurements (i.e. ΔT0-T20, ΔT20-T40 etc.) to see how change in posture could affect the time to maximum velocity. The delta values were calculated, and the results from the supine group were subtracted from the results from the upright group.

Power calculation: We expected a difference in time to inhibition of 15 min., a standard deviation of 10 min., risk of type 1 error of 0.05 and risk of type 2 error of 0.1. This yielded a sample size of seven. To reduce the risk of type 2 error, we chose to investigate 20 subjects.

Trial registration: This trial has been registered with clinicaltrials.gov (NCT01365741).

RESULTS

The baseline characteristics and values of the test group showed similarity (**Table 1**). The mean PRU value at baseline (T0) was 286 in the supine position and 272 in the upright position, (p = 0.6 for difference). The inhibition of thrombocyte function for the upright and the supine position appears from **Figure 1** and **Figure 2**. There was a statistically significant increase in inhibition of the ADP receptor in both the supine and the upright group from T = 40 to T = 100, when compared to T = 0 (p = 0.03 at T = 40 and p = 0.000 at T = 60/80/100).

When comparing the two groups, supine and upright, we saw a non-significant difference in baseline values of 15 PRU (standard error of mean = 26; p = 0.6). Since we were interested in the difference between the supine and the upright position, we adjusted for this difference. Thus, we found a significant difference between the supine and the upright group at T = 40 min. (p = 0.050) but a non-significant difference at T = 60 min. and T = 80 min. (p = 0.052, and p = 0.066, respectively) (**Table 2**).

Our analysis of the difference in velocity of thrombocytic inhibition between the two postures showed the largest difference at T40-T20 (48 PRU) and a spike at T100-T80 (10 PRU). This means that the maximum effect of posture change was seen at 20-40 min. after ingestion. When looking at each group in isolation, the biggest change in PRU values was seen in the 40-60-min. range in the supine group (Δ56.85 PRU) and in the 20-40-min. range in the upright group (Δ101.9 PRU).

Comparing the mean PRU values between the two groups, it was seen that at T = 40 min., the PRU values in both groups were below the cut-off of 240 (229 PRU in the supine group versus 178 in the upright group).

The mean time to reach the PRU cut-off of ≤ 240 was 40 min. in the upright position and 48 min. in the supine position. The difference, however, did not reach statistical significance ($p > 0.05$).

DISCUSSION

Our data showed a statistically significant difference in the time to inhibition of thrombocytic ADP receptors when comparing ingestion in the upright and the supine position. We also observed a non-significant trend towards a faster likelihood of reaching the cut-off before interventional procedures. It has been shown that pre- and post-procedural platelet reactivity measured by VerifyNow has a prognostic significance for the development of procedural complications [5, 14-16]. The consensus reached concerning the VerifyNow machine is that a pre- and post PRU of ≥ 240 increases the risk of post- and perioperative complications [5, 6, 8, 14, 17]. Sibbing et al investigated thrombocytic inhibition using a somewhat similar POC assay (Multiplate, Roche Diagnostics Limited) to define a cut-off for procedural complications. They: "did not observe a gradual increase of events across quintiles but a significant accumulation of stent thrombosis in patients belonging to the upper quintile of MEA (Multiple Electrode Aggregometry) measurements" [15], underlining the importance of proper thrombocytic inhibition prior to PCI.

VerifyNow was chosen because of its rapid results, easy handling and proven prognostic value in the evaluation of PCI patients [5, 6, 14, 16, 17]. VerifyNow has a good correlation to light transmission aggregometry (LTA) and vasodilator-stimulated phosphoprotein phosphorylation. It is shown to be reliable in the evaluation of platelet inhibition [18, 19], even in the upper and lower quartiles of inhibition.

One of the potential strengths of this study is the use of prasugrel instead of clopidogrel as the drug of choice. Prasugrel has a more consistent pharmacodynamics profile with improved efficacy and less interindividual variability. Studies have shown a non-responder rate using clopidogrel in the 0-52% range, but only about 3% have been reported to be non-responders to prasugrel [20]. In our study, 15% of samples (three measurements in the upright group and three measurements in the supine group) did not reach the cut-off during the 100 min. Had the sampling continued, the test subject might have had shown sensitivity to the drug later, but with regards to this study, they were "non-responders", thus weakening our result. Currently, a newer platelet inhibitor, ticagrelor (Brilique), has been introduced to the Danish market, but at the time of protocol approval, prasugrel was the preferred agent and, as described above, it showed potential strengths compared with clopidogrel and was thus our drug of choice for this randomised study.

The weakness of this study is first and foremost the small sample size. Using a cross-over study has potentially limited the effect of this weakness and increased the study's statistical strength. Prasugrel is a pro-drug needing gastric absorption and hepatic metabolism to become activated, but our subjects did not fast before the experiment, which might have influenced our results. Our test subjects were all young, healthy males.

FIGURE 1

Mean P2Y12 reaction unit (PRU) values adjusted for baseline difference.

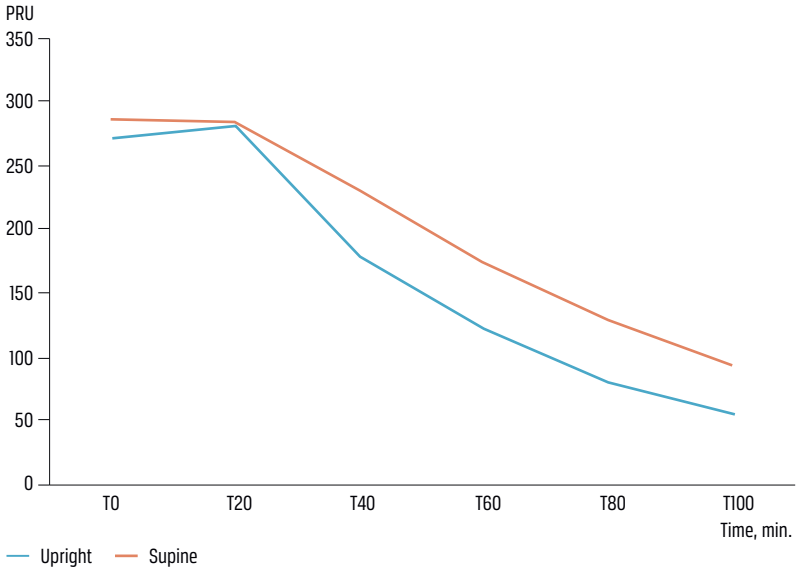
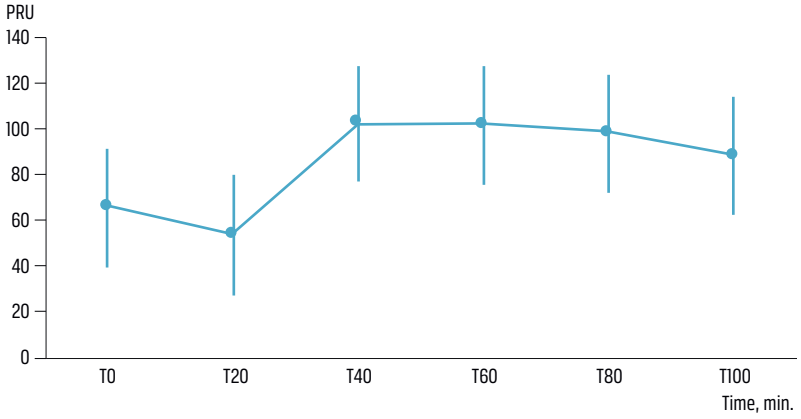


FIGURE 2

Mean difference in P2Y12 reaction units (PRU) between supine and upright with standard error of the mean.



Therefore, the results cannot be directly transferred to patients with acute cardiac ischaemia.

Seeing that prasugrel is prone to give PRU values in the upper quartiles of inhibition, one might suspect that the VerifyNow would be less reliable due to its narrow dynamic range. Studies have been conducted showing a good correlation between LTA and VerifyNow using prasugrel [19], even in the upper and lower quartiles of inhibition. This could possibly constitute a confounder in our study when looking at the overall difference between the supine and the upright position. Nevertheless, when looking at the velocity of inhibition in the mid quartiles of inhibition, this should have no effect on our results.

CONCLUSIONS

Our study showed a non-significant trend towards a faster reduction of platelet reactivity when ingesting prasugrel in the upright position than in the supine position. Larger clinical trials would be needed to confirm and assess the impact of posture on pharmacokinetics and its variability.

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